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Genetics of Sporadic Cerebral Amyloid Angiopathy

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1. Introduction

Cerebral amyloid angiopathies (CAA) can be divided into sporadic and hereditary forms. This chapter is focused on the genetics of sporadic CAA, but will first consider hereditary forms in brief.

1.1. Hereditary CAA

Amyloid- β protein ($A\beta$), the commonest amyloid subunit implicated in sporadic forms of CAA, is also involved in certain hereditary forms. Several other proteins are also associated with rare familial diseases in which CAA is a characteristic morphological feature. [1] Missense mutations within or just outside the $A\beta$ peptide coding region of the APP gene result in clinicopathological phenotypes of early onset Alzheimer's disease (AD) and are associated with a neuropathological phenotype which includes prominent CAA – for example hereditary cerebral haemorrhage with amyloidosis of Dutch type (HCHWA-D), or with Italian, Arctic, Iowa, Piedmont and Flemish mutations. Severe $A\beta$ CAA has also been well documented in cases of familial AD due to mutations in the presenilin (PSEN1 and PSEN2) genes. Familial CAAs associated with other proteins include BRI2 gene-related dementias (familial British dementia and familial Danish dementia), cystatin C gene mutations in hereditary cerebral haemorrhage with amyloidosis of Icelandic type, TTR gene mutations in meningo-vascular amyloidosis, hereditary prion disease with premature stop codon mutations and mutated gelsolin gene in familial amyloidosis of Finnish type. [1]

1.2. Sporadic CAA

Sporadic cerebral amyloid angiopathy is characterised by deposition of $A\beta$ in leptomeningeal and cortical blood vessels. It has a prevalence in population-based autopsy studies of 20-40%

in non-demented and 50-60% in demented elderly people. [2] Neuropathological case-control and cross-sectional studies, as well as the increased incidence of intracerebral haemorrhage (ICH) in patients with Alzheimer's disease, suggest that CAA causes lobar ICH. [3, 4] CAA is also associated with increasing age, dementia, lobar brain microbleeds, leukoaraiosis, small cortical infarcts and superficial siderosis. [3, 5-7]

It is unknown why only a few people with CAA pathology develop an ICH, but it seems likely to involve biological pathways additional to and distinct from those involved in vascular amyloid deposition. Cases of CAA with ICH not only have a greater proportion of amyloid-laden blood vessels, [8] but also more often demonstrate severe CAA with associated vasculopathy. [8-11]

Identifying genetic polymorphisms associated with the presence of histopathologically confirmed CAA in general, as well as with the severe form of CAA thought to cause vessel rupture and ICH, should increase our understanding of the mechanisms leading to CAA and associated diseases, including CAA associated ICH.

Polymorphisms in the apolipoprotein E gene (APOE) [12] are associated with ICH as well as with other conditions in which CAA may be involved, including subarachnoid haemorrhage, lobar brain microbleeds, and AD. [7, 13-18] In vitro studies have shown that APOE influences A β conformation, fibril formation and toxicity, [19, 20] while in vivo mouse studies have confirmed a critical role for apolipoprotein E in A β deposition, toxicity and possibly clearance. [21, 22] It therefore seems likely that APOE influences risk of developing histopathologically confirmed, sporadic CAA. Other genetic polymorphisms are also likely to contribute to development of sporadic CAA.

Below we present and summarise the evidence for associations of polymorphisms in APOE or any other gene with histopathologically confirmed, sporadic CAA in adult humans. We then go on to consider the evidence for associations of APOE with the severe form of CAA. The evidence presented is based mainly on our two recently published systematic reviews of all relevant published studies, both of which incorporated a comprehensive search strategy, a thorough assessment of study quality, a series of meta-analyses, and an evaluation of the robustness of any positive findings to small study and other methodological biases. [23, 24] Figure 1 summarises the strategy used for identifying relevant studies and the numbers of studies (and study participants) identified.

2. Genetic associations with histopathologically-confirmed, sporadic CAA

While robust, large-scale evidence exists for an association of APOE with ICH attributed to CAA on the basis of clinical criteria, [15] studies assessing association of APOE with histopathologically confirmed CAA have had various methodological shortcomings (including small size), and reported results vary. Our systematic review of genetic associations with histopathologically confirmed, sporadic CAA sought all studies in which participants had been

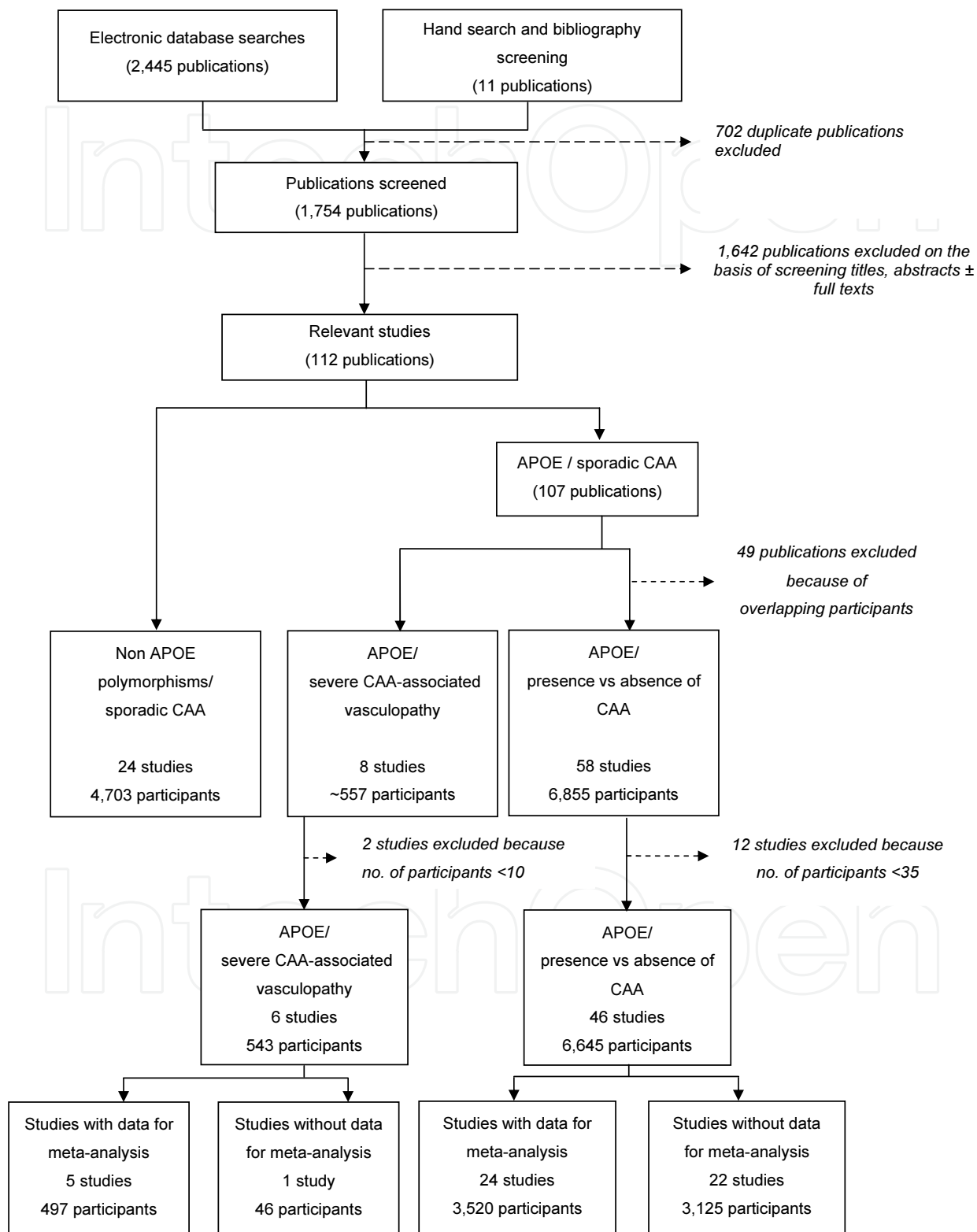


Figure 1. Selection of included studies

genotyped for any genetic polymorphism and had CAA assessed pathologically (using autopsy or biopsy). [23] Studies that had assessed genetic associations with CAA-associated ICH (CAAH) versus CAA-free controls were excluded, because these would not be able to distinguish a genetic association with the presence of CAA histopathology from an association with ICH.

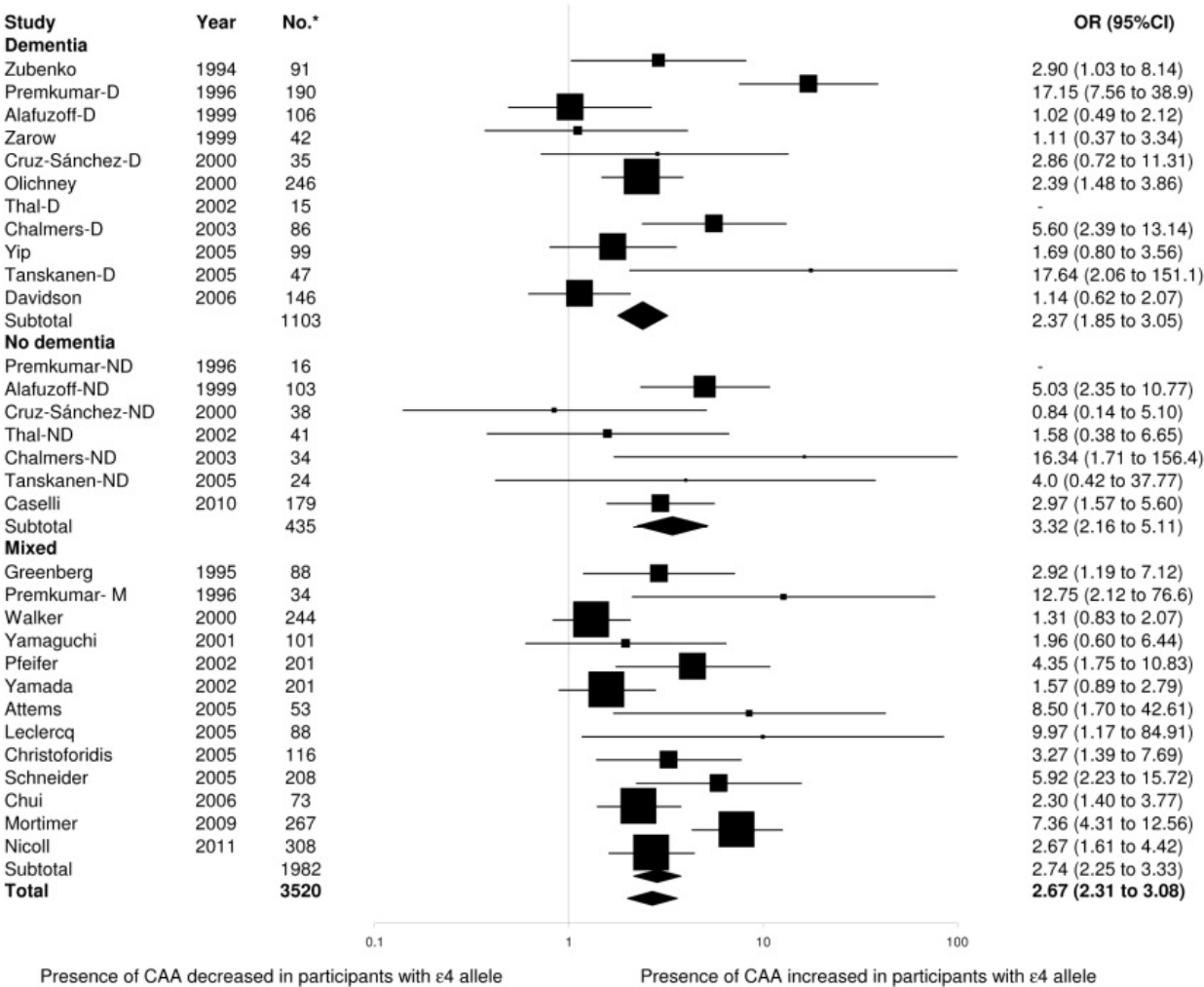
2.1. APOE $\epsilon 2/\epsilon 3/\epsilon 4$ polymorphism and sporadic CAA

We identified 46 studies including 6645 participants with data about the APOE $\epsilon 2/\epsilon 3/\epsilon 4$ polymorphism and sporadic CAA (Figure 1). [25-70] These studies had used autopsy brains from clinical autopsy collections, a brain bank or a population-based prospective study. Participants' mean age was 70 to 85 years in most studies and about half were male. Almost 90% of participants were of European ancestry while around 10% were from Asian populations (all Japanese). About 30% of participants had clinical dementia (mainly AD), about 10% were known not to be demented and dementia status was not specified for the remainder. There was substantial variation in overall study quality. Genotyping reporting quality [71, 72] was generally limited and methods for pathological assessment were very variable. Larger studies tended to be of higher quality. [23]

2.1.1. APOE $\epsilon 4$ and CAA

Meta-analyses were possible of data from just over half of these studies (including just over half of the participants), and showed a significant association between $\epsilon 4+$ genotypes and presence of CAA (OR 2.67, 95% CI 2.31 to 3.08), although there was significant heterogeneity between the studies' results (Figure 2). There were no significant differences between subgroups of studies based on dementia status, ethnicity or overall study quality score (Figures 2 and 3). Six studies (443 participants) made only a qualitative statement, [27, 30, 33, 37, 40, 42] reporting either no significant association or a trend towards association with APOE $\epsilon 4$, while 16 studies (2682 participants) provided no information about the association. [25, 28, 29, 31, 32, 34-36, 38, 39, 41, 43, 46, 47, 50, 57]

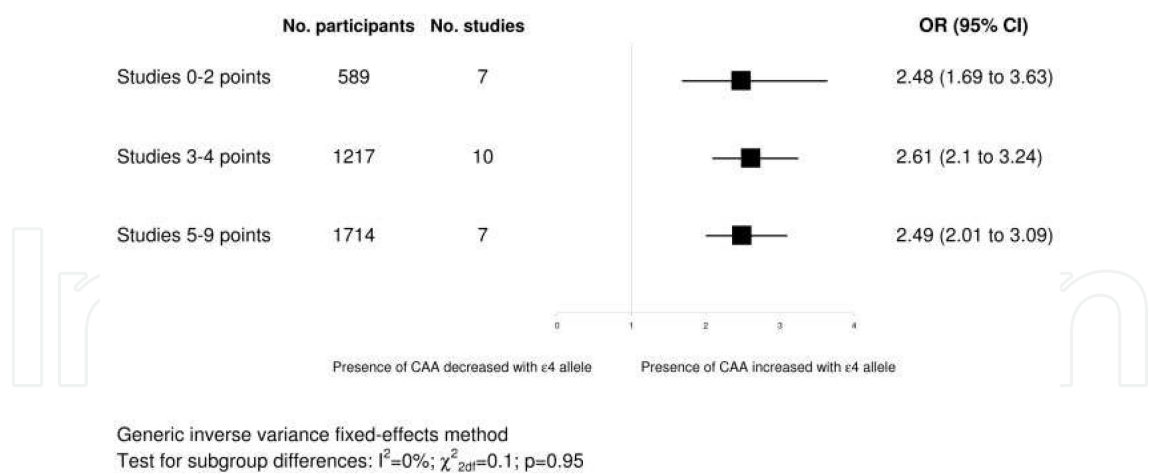
Failsafe N calculations [73] showed that a null study of >137, 000 participants would be required to bring the association of $\epsilon 4+$ genotypes with CAA from the meta-analysis to a just statistically non-significant level. This makes it unlikely that there might plausibly be enough participants in unpublished, unreported or otherwise unretrieved null studies to make this significant result non-significant, and suggests that the association of APOE $\epsilon 4+$ genotypes with histopathologically confirmed, sporadic CAA is real and robust. Meta-analysis of the association of APOE $\epsilon 4$ allele dose with CAA among 12 studies (1706 participants) providing quantitative data showed a significant increase in the odds of having CAA with increasing dose of the $\epsilon 4$ allele (Figure 4). Two further studies (117 participants) provided a qualitative statement about the association supported this result. [40, 64] Failsafe N calculations showed that it would require a null study of >7000 participants to bring the stronger association with CAA of $\epsilon 4$ homozygous versus heterozygous genotypes to a just non-significant level, suggesting that the finding of a dose-response relationship between APOE $\epsilon 4$ and CAA is real and robust.



Generic inverse variance fixed-effects method; p (overall effect) <0.00001
Tests for heterogeneity: $I^2 = 69\%$; $\chi^2_{28df} = 89$; p <0.00001
Tests for subgroup differences: $I^2 = 0\%$; $\chi^2_{2df} = 1.9$; p = 0.38
*Refers to number of participants included in analysis; 10 participants excluded because of missing data:
Christoforidis 2005 - 2 participants; Greenberg 1995 - 5 participants; Nicoll 2011 - 2 participants, Olichney 2000 - 1 participant.
D=clinically demented participants, ND=clinically not demented participants, M=demented and not demented participants

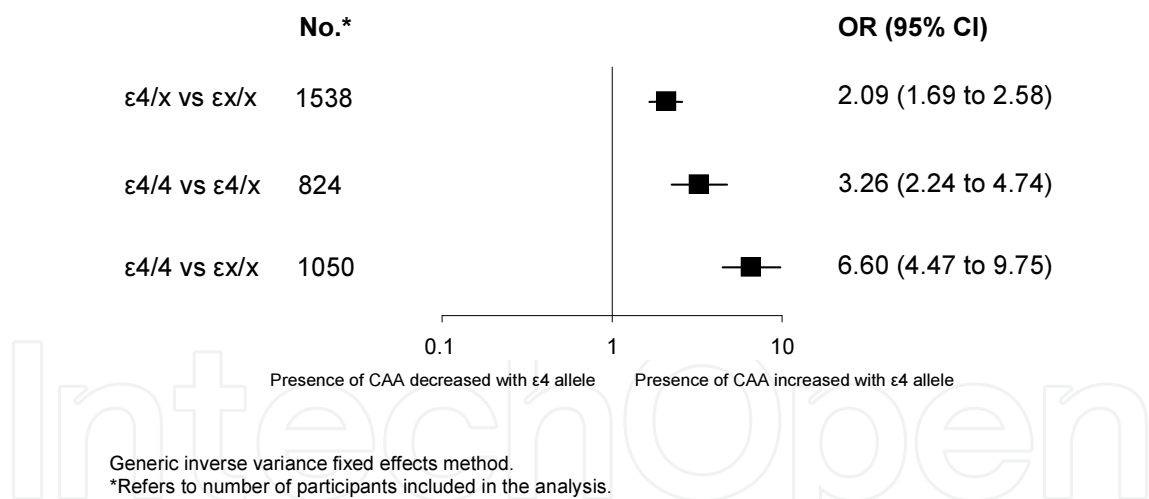
The squares represent study-specific odds ratios (ORs), with their size proportional to their statistical weight by the generic inverse variance method. Horizontal lines represent 95% confidence intervals (CIs). Diamonds represent pooled ORs, and their width represents the 95% CI. Higher score represents better study quality.
Reproduced from "Genetics of cerebral amyloid angiopathy: systematic review and meta-analysis" Rannikmäe K, Samarasekera N, Martínez-González NA, Al-Shahi Salman R, Sudlow C. Journal of Neurology Neurosurgery and Psychiatry 2013;84(901-8), with permission from BMJ Publishing Group Ltd.

Figure 2. Meta-analysis of association of APOE ε4+ vs ε4- genotypes with CAA by participants' dementia status



The squares represent pooled ORs and their width represents the 95% CI. Higher score represents better study quality. Reproduced from “Genetics of cerebral amyloid angiopathy: systematic review and meta-analysis” Rannikmäe K, Samarasekera N, Martínez-González NA, Al-Shahi Salman R, Sudlow C. Journal of Neurology Neurosurgery and Psychiatry 2013;84(901-8), with permission from BMJ Publishing Group Ltd.

Figure 3. Subgroup analysis based on study quality scores.



The squares represent pooled ORs and their width represents the 95% CI.

Figure 4. Meta-analysis of effects of APOE ε4 dose (ε4--/ε4+/-/ε4++ genotypes) on presence vs absence of CAA

2.1.2. APOE ε2 and CAA

Meta-analysis of the association of APOE ε2+ versus ε2- genotypes with CAA among 11 studies (1640 participants) showed borderline significant decreased odds of CAA with APOE ε2+ genotypes (OR 0.73, 95% CI 0.53 to 1.00, $p=0.05$). Two studies (213 participants) provided a qualitative statement; neither reported a significant association. [60, 64]

2.1.3. Summary and discussion

There is, therefore, robust evidence for a highly significant, dose-dependent association between APOE $\epsilon 4$ and pathologically proven CAA, which does not vary significantly with dementia status, ethnicity, or study quality. However, there is no clear overall association between APOE $\epsilon 2$ and histopathologically confirmed CAA. Lack of variation in the effect of APOE $\epsilon 4$ by study size and the very large failsafe N showed that this association could not plausibly be explained by publication, reporting or any other small study bias. It is important to note that the quality of studies included in our systematic review was generally limited when assessed against current reporting standards. [71, 72] However, there were - reassuringly - no significant subgroup differences by study quality score.

The prevalence of CAA in Alzheimer's disease is over 70% but the relationship between CAA and AD is still poorly understood. Although the diagnostic criteria for dementia and the participant inclusion criteria varied between the studies in our systematic review (some excluding cases with severe dementia), the demonstration of a similar association in those with and without clinical dementia suggests that the association of APOE $\epsilon 4$ with CAA is independent of its known association with dementia (mainly Alzheimer's disease).

Pathological assessment in the included studies was very variable. Indeed, there is no widely accepted, standardized histopathological grading system for CAA, [74] and no comparative studies to determine the most accurate method for assessing CAA (although the suggested method is a combination of Thioflavin S/T or Congo Red with immunohistochemistry). [75] CAA assessment location also varied widely, possibly influencing the rate of CAA detection, since a greater burden of CAA is generally reported in the occipital or parietal lobes, albeit with a higher frequency of frontal lobe involvement reported in studies from China and Japan. [74] This is important because genetic associations may differ by CAA location and subtype. For example, there is preliminary evidence that APOE $\epsilon 4$ may be associated with CAA type 1 (where CAA is found in cortical capillaries), and $\epsilon 2$ with CAA type 2 (where amyloid is deposited in leptomeningeal and cortical vessels with the exception of cortical capillaries). [26] In addition, since APOE effects on ICH may vary with ethnicity, there may also be ethnic variation in genetic associations with CAA, but these have not yet been widely enough studied in non-white populations to assess this reliably. [76]

2.2. Associations between other genetic polymorphisms and sporadic CAA

In our systematic review, few polymorphisms other than APOE had been studied in more than a few hundred participants or in more than one study and there were not enough data for meta-analysis (Figure 1, Table 1). [39, 46, 50, 61, 63, 77-95] Thus, there were too few studies and participants to draw firm conclusions about the effect of other genetic polymorphisms. However, there were some suggestive positive associations with CAA. First, there was a consistent trend towards an association with CAA of a single nucleotide polymorphism (SNP) in the transforming growth factor- $\beta 1$ (TGF- $\beta 1$) gene in two studies (449 participants). [82, 85] If real, this may occur through an influence of TGF- $\beta 1$ on A β clearance and deposition through activation of astrocytes and microglia. Second, there were significant associations in one study (723 participants) of SNPs in the translocase of outer mitochondrial membrane 40 (TOMM40)

gene with vascular amyloid burden but not with ICH attributed to CAA, [88] which could be through interaction of TOMM40 with APOE ε2 or through its effects on Aβ mitochondrial transport. Finally, one study (544 participants) found an association of a SNP in the complement component receptor 1 (CR1) gene with both CAA severity and ICH attributed to CAA, possibly occurring via altered clearance of Aβ peptide. [96] Other studies found no overall significant associations, although some reported associations in particular subgroups (Table 1).

Gene	Location / Polymorphism	No. of studies	No. of participants	Summary of results
TGF-β1	rs1800470	2	449	Consistent trend for positive association between T allele and CAA
TOMM40	rs2075650, rs34404554, rs11556505, rs769449, rs12972156, rs12972970, rs157582, rs184017, rs157581, rs283815, rs157580, rs439401, rs34095326, rs10119	1	723	SNPs associated with vascular amyloid burden
CR1 gene	rs6656401	1	544	Associated with severity of CAA pathology
LRP1 (low-density lipoprotein receptor 1)	rs1799986	3	597	
ACT (α1 antichymotrypsin)	signal region of the gene → A/T alleles that determine the aminoacid alanine or threonine**	2	235	
CYP46	rs754203	2	524	
ACE (angiotensin 1 converting enzyme)	intron 16 insertion/deletion of a 287 bp sequence	2	239	No overall significant associations (inconsistent trends and
Gene	PS1 (presenilin-1);BCHE (butyrylcholinesterase);DXS1047 locus;APOE promoter;A2M (α2 macroglobulin);PON1 (paraoxonase);NEP (neprilysin);OLR1 (oxidized low-density lipoprotein receptor 1);LRP (low density lipoprotein receptor related protein);CYP46; CH25H*1;VEGF (vascular endothelial growth factor);IL-1A;IL-1B;IL-33;GSTO1-1 (glutathione S-transferase omega-1);SORL1 (sortilin related receptor);CTSD (cathepsin D); AβPP and AβPppromoter;	18	50-380*	in some cases associations in subgroups)

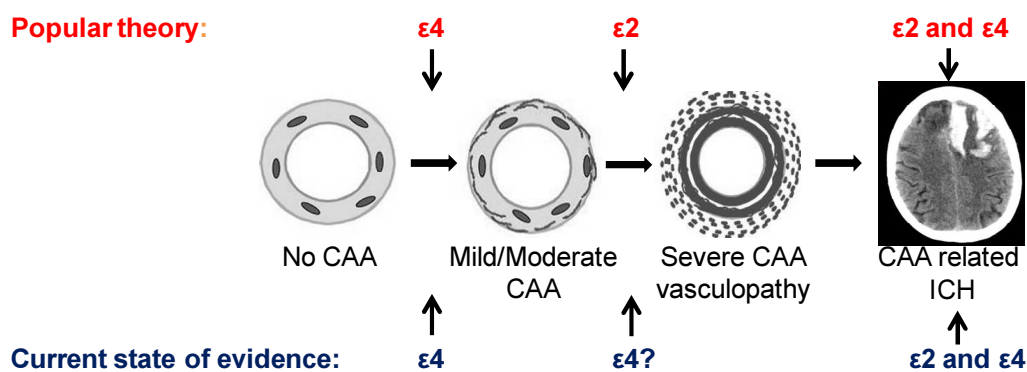
*Range of participant numbers in individual studies **probably rs4943

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Table 1. Summary of studies of non-APOE polymorphisms and CAA

3. APOE allele-specific associations with severe CAA-associated vasculopathy

The systematic review and series of meta-analyses presented in the previous section confirmed an association between histopathologically diagnosed CAA and APOE $\epsilon 4$, but not APOE $\epsilon 2$. However a recent large scale genetic association study found that both $\epsilon 2$ and $\epsilon 4$ containing genotypes were associated with clinically diagnosed CAA, manifesting as lobar ICH attributed to CAA. [15] Furthermore, APOE $\epsilon 2$ has been found to predict initial haematoma volume, haematoma expansion, increased mortality and poor functional outcome after lobar ICH. [17, 97] The currently favoured popular explanation for these findings is, that APOE $\epsilon 4$ enhances deposition of amyloid- β in cerebral blood vessel walls, while $\epsilon 2$ promotes haemorrhage from amyloid-laden blood vessels by increasing specific CAA-related vasculopathic changes (Figure 5). [8, 25, 98]



Adapted from Figure 1 in Acta Neuropathologica 2005;110: 345–359 “Sporadic cerebral amyloid angiopathy: pathology, clinical implications, and possible pathomechanisms”, Johannes Attems, with kind permission from Springer Science and Business Media and Professor Attems.

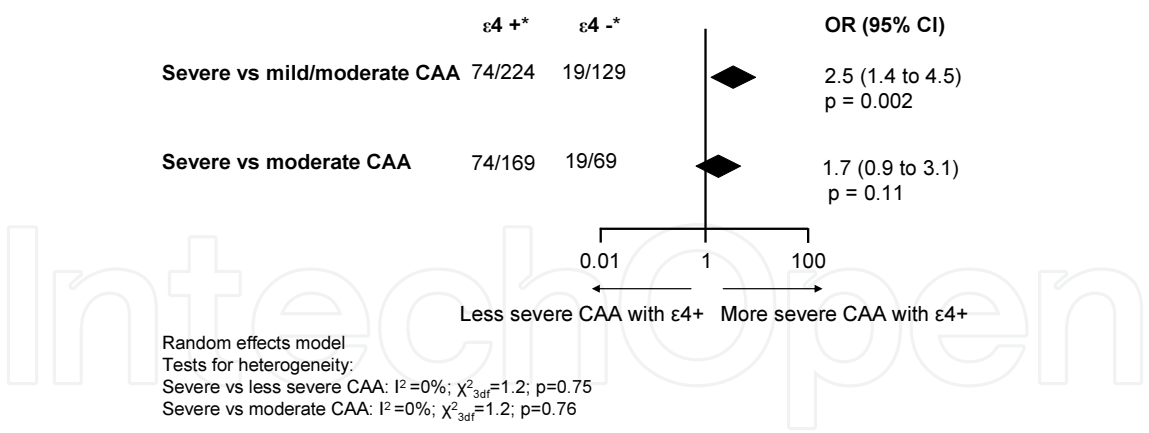
Figure 5. Proposed theory and current state of evidence about associations between APOE and CAA phenotype

In a further recent systematic review, we reviewed the evidence for this hypothesis. [24] The main focus of this work was on assessing the potential influence of APOE genotypes on severe CAA preceding rupture. To avoid selection bias, we excluded studies with participants selected on the basis of having had a CAA-related ICH, since APOE $\epsilon 2$ and $\epsilon 4$ are already known to be associated with this phenotype, and severe CAA is commoner in such cases. This review sought all studies, which had conducted both APOE genotyping and histopathological assessment for CAA, including assessment for severe CAA with associated vasculopathic

changes (blood vessel dilatation, microaneurysm formation, fibrinoid degeneration, cracking and double-barrelling of the vessel wall, and paravascular leakage of blood). The assessment for this severe form of CAA could have occurred either as part of the Vonsattel grading scale, [9] which includes such changes in its 'severe' category or through specifically reporting on some or all of the relevant histopathological characteristics. From 1754 publications screened, we identified six eligible studies, which included 543 eligible participants (Figure 1). [8, 25, 62, 64, 99, 100] Only one of the six studies had previously reported on the association between the APOE genotype and severe CAA (assessed using Vonsattel scale), finding a significantly greater frequency of APOE $\epsilon 2$ in severe versus moderate CAA cases. [25] This study and four others that had rated CAA on the Vonsattel scale, between them including 497 eligible participants (92% of all 543 potentially eligible participants), [62, 64, 99, 100] were able to share their unpublished data for collaborative meta-analyses.

The five studies included in the meta-analyses used autopsy brains either from brain tissue banks or from a population-based prospective study with an autopsy component. There were 57 to 227 eligible participants per study, mean age at death was 78 to 84 years and about half of all participants were male. Three studies (357 participants) were conducted in predominantly white populations in the USA while information on ethnicity was unavailable for two studies (140 participants). About 50% of participants had clinical dementia (mainly neuropathologically confirmed AD), about 20% were known not to be demented and in the remaining 30% dementia status was unknown. The quality of genotyping and of pathology assessment was generally very good when assessed against current reporting standards. [71, 72] As in the first of our two systematic reviews, methods for pathological assessment were variable, reflecting a lack of agreed standards for CAA pathology assessment at the time these studies were conducted. [24]

Among the 353 individuals in these five studies who had CAA present on histopathological assessment, meta-analyses found a significant association of $\epsilon 4+$ versus $\epsilon 4-$ genotypes with severe versus mild/moderate CAA (OR 2.5, 95% CI 1.4 to 4.5, $p=0.002$) but no significant association with severe versus moderate CAA (OR 1.7, 95% CI 0.9 to 3.1, $p=0.11$) (Figure 6). There was no significant heterogeneity between individual studies' results. For $\epsilon 2+$ versus $\epsilon 2-$ genotypes, the associations with severe CAA versus mild/moderate CAA and with severe versus moderate CAA were non-significant, with wide confidence intervals due to small numbers of participants, particularly in the $\epsilon 2+$ group, which included 22 individuals, only seven of whom had severe CAA (Figure 7). There was moderate heterogeneity between individual studies' results for severe versus mild/moderate CAA ($I^2=52\%$; $\chi^2_{3df}=6.2$; $p=0.1$) and minimal heterogeneity for severe versus moderate CAA ($I^2=11\%$; $\chi^2_{3df}=3.4$; $p=0.3$). Results were similar and conclusions unchanged for the $\epsilon 4+$ and $\epsilon 2+$ genotypes when $\epsilon 3\epsilon 3$ genotypes were used as the comparison group (rather than $\epsilon 4-$ or $\epsilon 2-$). Associations with the presence versus absence of CAA were consistent with results from the previous published systematic review [23], showing a clearly significant association with $\epsilon 4+$ ($\epsilon 4+$ versus $\epsilon 4-$: OR 4.8, 95% CI 3.0 to 7.6, $p<0.00001$) but not with $\epsilon 2+$ genotypes ($\epsilon 2+$ versus $\epsilon 2-$: OR 0.38, 95% CI 0.1 to 1.0, $p=0.05$).



The diamonds represent pooled OR across studies and the width of the diamonds represents 95% confidence intervals (CIs).

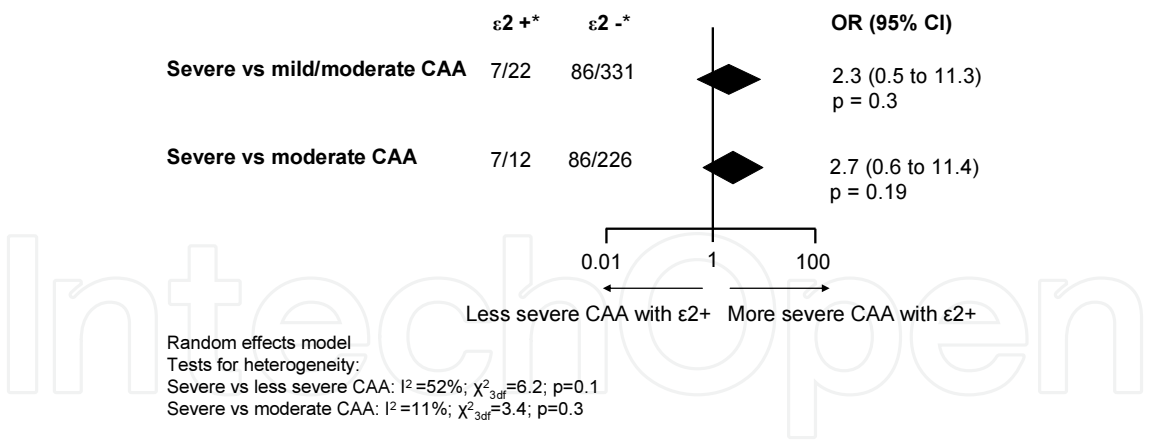
* $\epsilon 4 +$: number of subjects with an $\epsilon 4$ allele and severe CAA / total number of subjects with an $\epsilon 4$ allele and any severity of CAA or severe/moderate CAA

$\epsilon 4 -$: number of subjects without an $\epsilon 4$ allele and severe CAA / total number of subjects without an $\epsilon 4$ allele and any severity of CAA or severe/moderate CAA

Results of two studies conducted in one centre were combined for the analyses. [25, 64]

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Figure 6. Meta-analysis of APOE- $\epsilon 4$ associations with severe CAA



The diamonds represent pooled OR across studies and the width of the diamonds represents 95% confidence intervals (CIs). * $\epsilon 2 +$: Number of subjects with an $\epsilon 2$ allele and severe CAA / total number of subjects with an $\epsilon 2$ allele and any severity of CAA or severe/moderate CAA $\epsilon 2 -$: number of subjects without an $\epsilon 2$ allele and severe CAA / total number of subjects without an $\epsilon 2$ allele and any severity of CAA or severe/moderate CAA. Results of two studies conducted in one centre were combined for the analyses. [25, 64]

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Figure 7. Meta-analysis of APOE $\epsilon 2$ associations with severe CAA

Thus, contrary to what has been suggested, [8, 25] a systematic assessment of the relevant evidence suggests a possible association of APOE $\epsilon 4$ but not of APOE $\epsilon 2$ with progression to severe CAA (Figure 5). However, this does not exclude a biologically meaningful association with APOE $\epsilon 2$ since, despite including data from almost all relevant cases from the published literature, total numbers of individuals included in our meta-analyses were relatively small and confidence intervals wide, especially for analyses of the effects of APOE $\epsilon 2$. There were other limitations too. First, methods for histopathological assessment varied between studies, potentially introducing heterogeneity and reducing the likelihood of detecting a consistent effect across studies. Second, APOE allele-specific effects on severe CAA may differ according to the presence or absence of Alzheimer's disease, particularly for APOE $\epsilon 2$, which has been associated with a decreased risk of Alzheimer's dementia. [101] Informative subgroup analysis to explore potential causes of heterogeneity could not be performed, however, because of the small overall numbers of participants and because dementia status was unknown for a large number of participants. Third, while the studies included assessed those severe CAA-associated vasculopathic changes that are specifically alluded to in the Vonsattel scale, other vasculopathic changes may also be relevant. Fourth, both APOE allele-specific and other genetic associations may differ by CAA subtype. The preliminary evidence that APOE $\epsilon 4$ may be associated with CAA type 1 (where CAA is found in cortical capillaries), and $\epsilon 2$ with CAA type 2 (where amyloid is deposited in leptomeningeal and cortical vessels with the exception of cortical capillaries) [26] suggests that CAA types 1 and 2 may represent different pathological entities, and – if so – the mechanisms and genetic risk factors for severe CAA and ICH could also differ. Finally, there may be other genetic influences that interact with APOE $\epsilon 2$ to increase risk of or protect against severe CAA and ICH.

4. Conclusions

There is strong evidence that APOE $\epsilon 4$ promotes cerebral amyloid angiopathy, and further evidence to suggest that $\epsilon 4$ may increase the risk of developing severe CAA among those with CAA. However, there is not convincing evidence to support the theory that APOE $\epsilon 2$ promotes progression to severe CAA-related vasculopathic changes so leading to vessel rupture and ICH. Much larger numbers of individuals will need to be included in CAA histopathology studies if reliable conclusions are to be drawn about the specific effects of APOE $\epsilon 2$, while bearing in mind that APOE genotype will not be the only genetic influence on CAA. Future research efforts in this area will also be helped substantially by the development and use of an internationally-agreed, standardised histopathological grading system for CAA (including assessment of CAA types 1 and 2), and by the consistent reporting of dementia – and specifically Alzheimer's disease – status [102] among individuals included in CAA histopathology studies.

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